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Dear Professor Lederberg,

As you may know, the World Health Organization as part of its programme of research in human reproduction, is supporting efforts to develop a variety of new, safe, acceptable and effective methods of fertility regulation.

Research sponsored to date in the area of development of contraceptive vaccines is summarized in the Fourth Annual Report of the WHO Expanded Programme of Research, Development and Research Training in Human Reproduction (see pages 51 - 55) which we are sending under separate cover. Infertility in humans attributed to immunological factors may serve as a useful model for the development of birth control vaccines. Towards this end a bank of sera from infertile men and women has been established in Aarhus, Denmark.

A cooperative study for collection and analysis of sperm antibodies was initiated about a year ago. The bank collects large serum samples (200 ml) from infertile women and men with various kinds of sperm antibodies, and these sera are then being tested in other laboratories by a large number of techniques which can be grouped into three categories:

1) conventional techniques for determination of sperm antibodies (various agglutination tests, tests for immobilization and cytotoxicity and immunofluorescent techniques;
2) new techniques with purified sperm antigens (mainly tests for antibodies against sperm enzymes);
3) various tests for antibodies against antigens from other parts of the reproductive system (such as ovum, trophoblast, decidua, FSH, LH and hCG).

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The philosophy of this first study has thus been to obtain sera with sperm antibodies of different specificities, detectable in conventional techniques, and to use these sera as reagents in a number of new techniques against purified sperm antigens and antigens from other parts of the reproductive system. It is now being considered to initiate a new programme, organized in a similar way by the serum bank, but based on a somewhat different philosophy with selection of patients instead of selection of sera. The aim of the proposed study should be to collect large serum samples from a highly selected group of women with unexplained infertility and then to look for all kinds of antibodies which might be thought to be able to cause infertility, i.e. antibodies against sperm, ova, trophoblast, decidua and various hormones. Obviously such an approach would be very costly, not only in money, but also in time and efforts in many laboratories. To avoid waste of efforts and discouragement of the investigators engaged in the project, it will be extremely important to have from the begining the optimal set up of the project.

The problems which have so far been considered are:

1) On which criteria should the patients for such a study be selected? According to the present ideas it would seem most proper to select women from couples with a long history of infertility in whom both the male and female partner have had no previous diseases affecting the genital system and seem absolutely healthy, their only abnormality being the infertility. A detailed clinical protocol for the physical and laboratory examinations of male and female partner should be worked out in collaboration with specialists in gynecology and andrology.

2) In case the results of such a study remain negative, how many patients should then be examined before the programme is cancelled? Obviously sera from only 10 or 20 patients would be too few to draw any conclusions, if nothing is found, and to continue to register negative findings in 500 or more serum samples should probably be considered waste of efforts. If the chance of finding a "hot" serum is assumed to be of the order of about 1% in each of the four main systems (sperm, ovum, trophoblast and decidua) a series of about 125 sera should give a 99% guarantee to find something in at least one of the systems. From a practical point of view it would also seem possible for the clinics and laboratories to cope with a series of this size, and it is therefore suggested to settle for about 150 sera.

3) How comprehensive should the testing of the sera be in order to cover all possibilities, which can be foressen today? As presently outlined the programme should include:

a) quantitative determination of IgG, IgM and IgA electrophoresis.

b) tests for sperm antibodies:

Agglutinating antibodies (macro- and microtechnique)
immobilizing & cytotoxic antibodies
antibodies detectable by IFT and immuno-peroxydase technique
antibodies against LDH-X
anti-hyaluronidase
anti-acrosin
antibodies against spermatozoa-coating antigens
antibodies against seminal plasma antigens

c) tests for anti-ovum antibodies

d) tests for anti-trophoblast activity

e) tests for antibodies to purified placental antigens

f) tests for anti-decidual antobodies

g) tests for anti-hormone antibodies:

anti-FSH
anti-LH
anti-hCG

h) tests for autoantibodies against various tissues

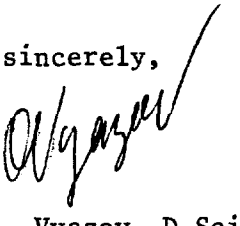
i) determination of HL-A antibodies and possibly also of activity in mixed leucocyte cultures

j) determination of blood groups and HL-A types.

We should appreciate if you would kindly consider the outlined project and give us your views on the rationale behind the programme and the validity you feel it might have. If you think it would be worth while to try this approach, would you then also give your comments with regard to the criteria for selection of patients, the number of patients to be tested if the various tests give negative results and the sufficiency of the tests listed.

Thanking you in advance for your cooperation we are looking forward to hearing from you.

Yours sincerely,



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